

## Editorial

# Human papillomaviruses and anal cancer

In 1793 Benjamin Bell wrote: "I have at present a person who had long been liable to piles, who some time ago was attacked with condylomatous excrescences from a venereal taint; to these succeeded a common abscess from inflammation, and last of all the parts have become cancerous."<sup>1</sup> During the last few years there has been a renewed interest in the relationship between anal cancer (squamous carcinoma of the anal margin or anal canal) and infection by human papillomaviruses (HPV). Anal cancer is a rare tumour, which in Britain accounts for only 2% of all anorectal malignancies.<sup>2</sup> A few years ago it was noted that its incidence was higher in single men, and in men who had reactive syphilis serology, than in married men.<sup>3,4</sup> This implied, although it did not prove, a relationship between the disease and anal eroticism in male homosexuals. Cases which appeared to support this hypothesis were reported by Cooper *et al*,<sup>5</sup> who had treated four homosexual men with cloacogenic carcinoma, and by Li *et al*,<sup>6</sup> who described squamous carcinoma of the anus in two homosexual men, one of whom gave a long history of anal condylomas. In a recent epidemiological study Daling *et al*<sup>7</sup> showed that in men a history of anoreceptive intercourse, and of genital warts, were strongly associated with the development of anal cancer. These reports awakened interest in the possibility of an oncogenic potential for HPV at the anus.

In heterosexual men and in women anal warts often accompany genital warts.<sup>8</sup> Warts confined to the anus and anal canal are commoner in homosexual men, in whom subclinical infections also occur.<sup>9,10</sup> The presumed mode of transmission of the causal agent is anal intercourse, which is admitted by 80% of men and women with anal warts,<sup>11</sup> but in homosexual men these are several times commoner than penile warts.<sup>11,12</sup> The reason for this discrepancy is unknown. It may be due to a preferential growth of condylomas in the moist conditions of the anus and anal canal. Alternatively, it has been suggested that the transitional zone, lying between the proximal rectal columnar mucosa and the squamous epithelium of the anal canal, may be analogous to the transitional zone of the cervix uteri, and be a favourable site for HPV infection.<sup>13</sup> Another possibility is that frequent anal intercourse leads to depressed immune responses which facilitate HPV

infection.<sup>14</sup> Studies of anal condylomas from homosexual men have shown a predominance of HPV 6 and 11, but sequences of HPV 16 are present in some lesions.<sup>15</sup>

There have been many case reports of anal intraepithelial neoplasia (AIN) Grade 3 (carcinoma in situ) within condylomatous tissue or in anal mucosa adjacent to it,<sup>16-19</sup> and malignant transformation of perianal condyloma acuminatum and giant condyloma have been described.<sup>20-22</sup> Gal *et al* identified papillomavirus antigens in five of eight squamous carcinomas of the anus from homosexual or bisexual men.<sup>23</sup> There have been several reports of sequences of HPV 16 in perianal and anal canal cancers.<sup>24-26</sup> This genotype is often associated with invasive cervical cancer and has been regarded as "high risk",<sup>27</sup> however, HPV 16 and 11, so-called "low risk" types, have been identified in a squamous carcinoma of the anus arising in a giant condyloma.<sup>22</sup>

Immunosuppression severely restricts the host's ability to control neoplasms induced by other causes. Penn<sup>28</sup> has reported a 100-fold increase in the incidence of carcinoma of the vulva and anus in renal allograft recipients compared with the general population. Warts, including anogenital warts, are also common in these patients.<sup>29</sup> Anogenital warts develop in many homosexual men with human immunodeficiency virus (HIV) infection.<sup>30,31</sup> Frazer *et al*<sup>13</sup> reported a high incidence of cytological changes suggesting both HPV infection and dysplasia of the anorectal epithelium among homosexual men with HIV infection and evidence of immune dysfunction (a low CD4/CD8 ratio). Croxson *et al*<sup>17</sup> described seven homosexual men with carcinoma in situ associated with anal warts, four of whom had AIDS-related symptoms, and Howard *et al*<sup>32</sup> described two cases of carcinoma of the anus in homosexual HIV-positive men with T-helper lymphocyte depletion, one of whom gave a long history of perianal warts.

How are the data relating homosexuality, HPV infection and anal neoplasia to be interpreted? Comparisons between the aetiology of carcinoma of the anus and carcinoma of the cervix should be made with caution. The epidemiological evidence implicating specific HPV types as a cause of cervical neoplasia has recently been criticised by Munoz *et al*<sup>33</sup> on the

grounds of small sample size, potentially biased selection of study subjects and the unknown sensitivity and specificity of the various hybridisation procedures for detecting DNA. Moreover, earlier studies have consistently underestimated the prevalence of HPV 16 in the normal cervix. Recent use of the polymerase chain reaction has shown that HPV 16 DNA is present in 80% of women with normal cytology;<sup>34</sup> clearly the relationship between HPV and cervical cancer is not as straightforward as it appeared to be a few years ago.<sup>35</sup> These observations apply with equal force to the problems surrounding anal neoplasia. We know very little about the epidemiology of anal HPV infection. The prevalence of infection of normal anal epithelia with HPV genotypes is unknown. Although HPV 16 has been identified in anal neoplasms the number of cases has been small and the studies either poorly controlled or not controlled at all. The most appropriate method of detecting HPV in anal specimens has not yet been decided. If specific HPV types are involved in anal neoplasia they would almost certainly be as necessary rather than sufficient causes; other factors, such as trauma, infection, antigen load and the subject's immune status are likely to be involved.

There is a real need for more studies of anal HPV infection and its relationship to neoplasia. These should include: (1) data on the prevalence of HPV genotypes in normal anal epithelia in homosexual and heterosexual men, (2) reassessment of the natural history of uncomplicated HPV infection in relation to clinical and subclinical lesions and infecting genotypes, (3) well designed case-control studies of the frequency of HPV genotypes in men with AIN and anal cancer, (4) prospective cohort studies of men with clinical and subclinical anal HPV infection, and (5) assessment of the results of treatment of HPV-associated lesions of the anus in patients with and without impaired immunity. Some of these problems are addressed in articles in this issue of *Genitourinary Medicine*. Syrjanen, Von Krogh and Syrjanen (p 216) have studied a series of condylomas obtained from homosexual and heterosexual men, seeking associations between their sexual orientation, their HIV status, the duration and morphology of the warts, the HPV types present and the degree of AIN observed. In most cases overt wart disease was associated with HPV 6 and 11; the "high risk" types HPV 16, 18, 31 and 33 were uncommon. AIN I-II was present in about 30% of lesions, but was not associated with any specific genotypes. McMillan and Bishop (p 225) studied the effect of HIV infection on the natural history of anogenital warts in men. Particularly in homosexuals, HIV infection was associated with a prolonged duration of the warts both before and after the initiation of treatment. Anal malignancy was not detected in any of the patients in this series, but in view of the current

uncertainty about the long-term effects of HPV infection, the authors are surely right to advocate regular examination of HIV-infected patients for early neoplasia of the anus and anal canal.

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